

REMARKS

At the outset, it is noted that a shortened statutory response period of three (3) months was set in the September 14, 2006 Official Action. The initial due date for response, therefore, was December 14, 2006. A petition for a two (2) month extension of the response period is presented with this Request for Reconsideration, which is being filed before the expiration of the two (2) month extension period.

It is also noted, preliminarily, that a complete claim listing has not been submitted with this Request for Reconsideration. According to the current PTO claim amendment practice, a complete claim listing is required only when changes are made to any claims. See, <http://www.uspto.gov/web/offices/pac/dapp/revised121gnas.htm>.

In the September 14, 2006 Official Action, the 35 USC §103 rejection of claims 1-18 is maintained from the previous Official Action, dated March 10, 2006, and made final. The rejection is based on the combined disclosures of JP 1005990, U.S. Patent 5,096,694 to Quivy et al. and Downer et al. (Nucl. Med. & Biol., 28: 613-26 (2001)). According to the examiner, it would have been *prima facie* obvious at the time the present invention was made, based on the combined disclosures of the above-cited references, to make a radio-labelled conjugate of thymidine and other bases containing phospho groups and dihydrotestosterone and use the same in a method of treatment and imaging of tumors and cancers as instantly claimed with a reasonable expectation of success, since such use is allegedly taught in the prior art.

The foregoing rejection constitutes the sole ground set forth in the September 14, 2006 Official Action for refusing the present application. The 35 USC §112, second paragraph, rejection of claims 1-18, which was the only other ground of rejection set forth in the preceding Official Action, is acknowledged to be "overcome by amendment to claim 1",

at page 2 of the September 14, 2006 Official Action.

In the response to the preceding Official Action, detailed arguments were presented establishing that the prior art of record fails to establish a *prima facie* case of obviousness. In view of the apparent deficiencies in the references cited as evidence of obviousness in this case, the undersigned initiated a phone interview with Supervisory Primary Examiner Jiang on or about November 3, 2006 and December 5, 2006 to request further review of the final rejection. It was pointed out to Supervisory Primary Examiner Jiang that if the PTO were prepared to take the final rejection to appeal, then applicants would file a Notice of Appeal promptly, rather than incur the needless expense of filing a Request for Reconsideration which, in all likelihood, would be fruitless. Supervisory Primary Examiner Jiang stated that she would review the final rejection and determine what course of further prosecution would be appropriate.

On or about December 8, 2006, Supervisory Primary Examiner Jiang called the undersigned and indicated that, upon the filing of a Request for Reconsideration, the final rejection would be withdrawn, prosecution would be re-opened and further examination would be undertaken, after which a new ground of rejection would be entered or the application would be allowed. The courtesy extended by Supervisory Primary Examiner Jiang in making the requested further review of the final rejection is sincerely appreciated.

As pointed out in Applicants' response to the preceding Official Action, the present invention provides cancer-specific radiolabeled conjugates that are designed to take advantages of two characteristics of many relapsing cancers, i.e. (1) the large portion of rapidly growing and dividing cells in relapsed/advanced cancers; and (2) the expression of androgen receptors in practically all prostate, ovarian and breast cancers. Upon administration, a conjugate of this invention first bind to the sex hormone binding globulin,

which in turn carries it exclusively to cells that have androgen receptors. After this cell-binding event, the entire conjugate is transported into the cell. Intracellular enzymes cleave the radiolabeled deoxyuridine analog from the dihydrotestosterone (DHT), thereby releasing and trapping within the cell the portion of the conjugate that is responsible for the cytotoxic effect. This cytotoxic effect is induced only when the cell cycle dependent therapeutic agent is incorporated into the DNA of dividing tumor cells. This dependence of radio-toxicity on the participation of the radiolabeled agent in DNA synthesis, in combination with relatively rapid pharmacokinetics, limits the exposure of normal tissue to radiation from the radionuclide. In other words, the conjugate that remains in systemic circulation, or enters normal tissue or organs, is essentially innocuous.

Because the references cited as evidence unpatentability, considered individually or together, neither teach nor suggest the structure of Applicant's cancer-specific radiolabeled conjugates, and their attendant advantages, as briefly outlined above, the cited references fail to provide a proper basis for rejecting Applicants' claims on obviousness grounds, as the following discussion will clearly demonstrate.

As noted by the Board of Appeals in *In re Wolters*, 214 U.S.P.Q. 735 (PTO Bd. Apps. 1979), the Examiner bears the initial burden of establishing a *prima facie* case of obviousness. When the Examiner fails to establish a *prima facie* case of obviousness, the rejection is improper. *In re Fine*, U.S.P.Q. 2d 1596 (Fed. Cir. 1988).

According to §706.02(j) of the Manual Patent Examining Procedure, ("Contents of a 35 U.S.C. 103 Rejection"), three basic criteria must be met in order to establish a *prima facie* case of obviousness, which are as follows:

"First, there must be some suggestion or motivation either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine the reference teachings. Second,

there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on Applicant's disclosure [citation omitted]."

Regarding the first criterion of *prima facie* obviousness, i.e. suggestion or motivation to combine the cited prior art disclosures, it is well settled that merely because it is possible to find isolated disclosures which might be combined in such a way to produce a new compound does not necessarily render such production obvious, unless the art also contains something to suggest the desirability of the proposed combination. *In re Bergel*, 130 U.S.P.Q. 206 (CCPA 1961). To the same effect is *Ex parte Hiyamizu*, 10 U.S.P.Q. 2d 1393 (P.T.O. BPAI 1988), in which the Board held that citing references that merely indicate that isolated elements and/or features recited in Applicants' claims are known is not a sufficient basis for concluding that a combination of the claimed elements would have been obvious.

In the present case, the Examiner is doing precisely what was held improper in *Bergel* and *Hiyamizu, supra*. Applicants' claims are directed to conjugates comprising component compounds, namely, radiolabeled deoxyuridine and DHT, which are chemically bound to one another. The Examiner has conceded that not one of the cited references discloses such conjugates. See the discussion of JP 10-059990, Quivy et al. '694 and the Downer et al. publication, at pages 4-5 of the preceding Official Action.

In the September 14, 2006 Official Action, the examiner does not deny these earlier acknowledgments, but instead argues in effect that the cited references disclose "pieces" of the claimed conjugates, and that these "pieces" somehow render obvious the conjugates, *per se*. Concerning JP 10-059990, the examiner asserts, at page 4 of the September 14, 2006 Official Action, that one of ordinary skill in the art will recognize that "a phospho substituted

sugar moiety can be used as a component in tumor imaging”. The examiner conveniently overlooks that JP 10-059990 is silent with regard to any DHT component of the disclosed uridine derivatives, and the way in which the radioactive metal nuclei are incorporated therein. However, the full text of JP 10-059990, an English language translation of which is submitted herewith, clearly shows that the radioactive metal nuclei, such as ^{99m}Tc , are complexed with the polyphosphate substituents of the sugar moiety, rather than substituted on the uracil base, as called for in Applicants’ claims. Indeed, the polyphosphate group is used specifically because of its “very strong chelating ability with respect to radioactive-labelled metal nuclei . . .” See last five lines of page 5 of the enclosed translation of JP 10-059990, as well as page 4, lines 1-3. Thus, it is clear that the uridine derivatives disclosed in JP 10-059990 form coordination complexes with the radioactive metal nuclei, rather than forming a covalent bond with a radionuclide, as in Applicants’ conjugates.

Given that the radioactive metal nuclei form a coordination complex with the phosphate residue of the uridine derivatives in JP 10-059990, it follows that none of those derivatives would be effective for participating in DNA synthesis. Moreover, the charge associated with the polyphosphate groups of the uridine derivatives described in JP 10-059990 will preclude the uptake of those derivatives into cells. Even if it were assumed that all cells have P1 and P2 purinergic receptors, the presence of the radiometal will render the derivatives described in JP 10-059990 unrecognizable by the receptors. The radiolabelled deoxyuridine component of Applicants’ conjugates, by contrast, are actively incorporated into the DNA of dividing cells.†

† Indicates argument which was not responded to in final rejection.

Furthermore, it is not understood why the examiner has focused solely on the phospho-substituted sugar moiety of JP 10-059990, while disregarding the radioactive metal nuclei that are complexed with the phospho substituents. The overall disclosure of JP 10-059990 certainly does not warrant such a limited focus. Given that the phospho substituents in JP 10-059990 are included because of their chelating ability with radioactive metal nuclei, it would appear that any modification of Quivy et al. that may be suggested by JP 10-059990 would also include the complexed radioactive metal nuclei, in which case the resulting nucleoside analog would, without question, be patentably distinct from Applicants' claimed conjugates, which are not complexed with a radioactive metal nuclei.

In short, those of ordinary skill in the art would not consider the disclosure of JP 10-059990, relating to radioactive metal nuclei-uridine coordination complexes, to be of any relevance or assistance when the objective is a cancer-specific radiolabeled conjugate regulated by the cell cycle for the treatment and diagnosis of cancer.

Turning to Quivy et al. '694, the examiner contends that this reference discloses conjugates of thymidine labelled with Auger-electron emitting isotopes like I123 which are attached to a deoxysugar. Here again, this constitutes only a "piece" of Applicants' claimed conjugates, as Quivy et al. '694 makes no mention of the chemical coupling of the thymidine analog to DHT as required in Applicants' claims. Moreover, the examiner's characterization of the compounds of Quivy et al. '694 as "conjugates" is a blatant mischaracterization. The reference itself refers to the disclosed compounds as "nucleotide analogs" which are defined (at column 2, lines 36-39) as "a substance having the structure of a natural nucleoside but in which the base of [sic or?] the sugar portion can have an unnatural substitution.

As for the Downer et al. publication, the examiner merely notes, with respect to the DHT "piece" of Applicants' conjugates, that it was found to have a high uptake by prostate at

one hour, and further that androgens are useful in the diagnosis and imaging of cancers and tumors.

The examiner summarizes the disclosures of the cited references, and the basis on which their combined disclosures allegedly render claims 1-18 *prima facie* obvious, as follows:

Quivy and the '990 patent may not teach conjugates as instantly claimed. But the fact that phospho substituted sugars that are structurally close to the one instantly claimed and radiolabeled dihydrotestosterone is found to have a high uptake by cancer cells as taught by Downer, suggests to one of ordinary skill in the art that phosphosugars can be used in imaging and dihydrotestosterone can be used as a carrier and a conjugate comprising both is also useful for imaging cancers and tumors.

One of ordinary skill in the art will be motivated to make a phospho containing thymidine or uridine with an Auger electron emitting radiolabel and dihydrotestosterone and use the same in a method for treating and imaging tumors and cancers since such a combination has the advantage of high uptake due to the presence of the dihydrotestosterone moiety and the cancer cell destroying and imaging ability because of the presence of the Auger electron emitting radioisotope in a single compound.

Hence, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to make a radio labeled conjugate of thymidine and other bases containing phospho groups and dihydrotestosterone and use the same in a method treatment and imaging of tumors and cancers as instantly claimed with a reasonable expectation of success since the use of such is taught in the prior art.

See pages 4-5 of the September 14, 2006 Official Action.

The fundamental flaw in the examiner's position is that none of the cited references provide any motivation whatsoever for chemically coupling the respective "pieces" to form a conjugate. In fact, the term "conjugate" does not appear in any of the cited references. That being the case, it cannot reasonably be maintained that JP 10-059990, Quivy et al. '694 and the Downer et al. publication, considered together, teach or suggest an essential feature of

Applicants' claims that none of those references teach separately, i.e., a radiolabeled conjugate of formula (I) (see claim 1), wherein B* represents uracil substituted with a radionuclide and at least one of R and R¹ comprises DHT. *Cf., Rockwell Corp. v. United States*, 47 USPQ 2d 1027, 1033 (Fed. Cir. 1998).†

Further in this regard, the examiner's assertion, at page 4 of the September 14, 2006 Official Action, that the combined disclosures of the cited references "suggest to one of ordinary skill in the art . . . dihydrotestosterone can be used as a carrier" grossly exaggerates the references' teachings. Although the Downer et al. publication may reasonably be regarded as disclosing dihydrotestosterone as a carrier for radiolabeled halogens, there is clearly nothing to suggest its use as a carrier for a radiolabeled uridine, as required in Applicants' claims. Neither the Downer et al. publication nor JP 10-059990 nor Quivy et al. '694 provide a proper factual basis for any broader interpretation of its disclosure.

In summary, the references cited as evidence of obviousness with respect to the subject matter of claims 1-18 fall far short of providing the motivation or suggestion to combine their teachings in the manner proposed by the Examiner. *Cf., Ex parte Levengood*, 28 U.S.P.Q. 2d 1300, 1301(PTO BPAI 1993). ("the only suggestion for the examiner's combination of the isolated teachings of the applied references improperly stems from appellant's disclosure and not from the applied prior art"). Consequently, the first criterion for a prima facie case of obviousness has not been established.

As for the reasonable expectation of success, it is evident that none of the cited references even remotely suggests that those of ordinary skill in the art should make Applicants' conjugates comprising radiolabeled uridine chemically bound to DHT, or that

† Indicates argument which was not responded to in final rejection.

those skilled in the art would have a reasonable expectation that such conjugates could be successfully made. Nor do the cited references teach or suggest that the resultant conjugates would have among their properties cancer cell specificity, together with cell cycle-dependent cytotoxicity, which are characteristics of Applicants' claimed conjugates.† Since Applicants' conjugates and their unique properties that make them effective for the treatment and/or imaging of cancer are nowhere suggested in the cited references, it necessary follows that the requisite reasonable expectation of success is lacking in this case.

It is noted in passing that the aforementioned properties of the claimed conjugates cannot be disregarded (as the examiner has done) in determining non-obviousness under 35 U.S.C. §103(a), since chemical compounds are inseparable from their properties, and thus constitute the subject matter "as a whole", which is the focus of the 35 U.S.C. §103(a) analysis.† *In re Albrecht*, 185 U.S.P.Q. 585 (CCPA 1975).

Turning to the third criterion of *prima facie* obviousness, the references proposed to be combined in this case clearly fail to teach or suggest all of Applicants' claim recitations. As noted above, there is no disclosure or suggestion of conjugates comprising radiolabeled deoxyuridine chemically bound to DHT, as claimed by Applicants herein.† Furthermore, the claims recite that DHT is bound in specific positions on the deoxyuridine moiety, i.e. as part of the R or R' groups.† The Examiner has offered no evidence or rationale as to how one would go about making the "radio labeled conjugate of thymidine and other bases containing phospho groups and dihydrotestosterone", as asserted at page 5 of the September 14, 2006 Official Action.† However, the test of any prior art relied on to show or suggest that a chemical product is unpatentable, is whether the prior art disclosure is such as to place the

† Indicates argument which was not responded to in final rejection.

claimed product in the possession of the public. *In re Brown*, 141 U.S.P.Q. 245 (CCPA 1964). It is beyond question in this case that the combined disclosures of JP 10-059990, Quivy et al. '694, and the Downer et al publication fail to put Applicants' claimed conjugates and their methods of use in the possession of the public.†

The Examiner's burden of providing factual support for an obviousness determination is not met by assuming the presence of claim recitations that are not found in the cited references. *Ex parte Wolters, supra*.

In view of the above-noted differences between the respective disclosures of the cited references, as well as the clear differences between such disclosures and the claimed invention, it is quite apparent that the Examiner has used Applicants' disclosure as a guide for combining unrelated prior art teachings in an effort to "piece together" the claimed conjugates, and in this way make out a case of *prima facie* obviousness. Such hindsight reconstruction of an invention has long been held impermissible, since it is contrary to the standard of obviousness set forth in 35 U.S.C. §103, which requires a determination of whether the claimed subject matter as a whole would have been obvious at the time the invention was made, based on the state of the art as reflected in the cited references, and without benefit of Applicants' disclosure. None of the references relied on by the Examiner in support of the §103(a) rejection of claims 1-18 contains the slightest suggestion of doing what the Applicants have done. It must be concluded, therefore, that the rejection is based on impermissible hindsight. *Cf., Ex parte Stauber*, 208 U.S.P.Q. 945(Bd. Apps. 1980).

For all of the foregoing reasons, the prior art references cited in support of the §103(a) rejection in this case neither teach nor suggest the claimed subject matter as a whole, and as

† Indicates argument which was not responded to in final rejection.

such, fail to establish that Applicants' invention is *prima facie* obviousness. Accordingly, the rejection of claims 1-18 under 35 U.S.C. §103(a) based on the combined disclosures of JP 10-059990, Quivy et al. '694, and the Downer publication is improper and should be withdrawn.

In view of the foregoing remarks, it is respectfully urged that the rejection set forth in the September 14, 2006 Official Action be withdrawn and that this application be passed to issue, and such action is earnestly solicited.

Respectfully submitted,

DANN DORFMAN HERRELL and SKILLMAN, P.C.

Attorneys for Applicant

By Patrick J. Hagan
Patrick J. Hagan
Registration No. 27,643

Customer Number 000110
(215) 563-4100 (telephone)
(215) 563-4044 (facsimile)
phagan@ddhs.com (email)

Enclosure: English translation of JP 01-059990

Translated from Japanese by
 SCIENTIFIC TRANSLATION SERVICES
 411 Wyntre Lea Dr.
 Bryn Mawr, PA 19010

(19) Japanese Patent Office (JP)

(12) Patent Disclosure Bulletin (A)

(11) Patent Disclosure No.: 10-59,990

(43) Patent Disclosure Date: March 3, 1998

| (51) | Int. Cl. ⁶ : | Identification Code | Internal File No. | FI | | Tech. Indic. |
|------|-------------------------|---------------------|-------------------|------------|-----|--------------|
| | C07F 13/00 | | | C07F 13/00 | | Z |
| | A61K 31/70 | ADU | | A61K 31/70 | ADU | |
| | 51/00 | | | C07F 5/00 | | D |
| | C07F 5/00 | | | 7/22 | | S |
| | 7/22 | | 7419-4H | C07B 59/00 | | |
| | // C07B 59/00 | | | A61K 49/02 | | A |
| | C07M 5:00 | | | | | |

Request for Examination: not yet made Number of Inventions: 9 FD (Total 6 pages)

(21) Patent Application No.: 8-231,275

(22) Patent Application Date: August 14, 1996

(71) Applicant: 000149837
 Daiichi Radio Isotope Laboratory
 1-17-10 Kyobashi, Chuo-ku, Tokyo

(72) Inventor: Hajime Kanbara
 16-94 Kumyo, Togane-shi, Chiba Pref.

(72) Inventor: Katsutoshi Tanaka
 1-A 50-7 Matsuo, Matsuo-cho, Sanmu-gun, Chiba Pref.

(72) Inventor: Toshiro Yamaguchi
 3-29-5 Minami Koiwa, Edogawa-ku, Tokyo

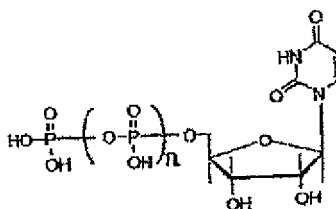
(74) Agent: Nobuo Ono, Patent Attorney

(54) Title of the Invention: **Radioactively Labeled Uridine Derivatives and Drugs Containing Same**

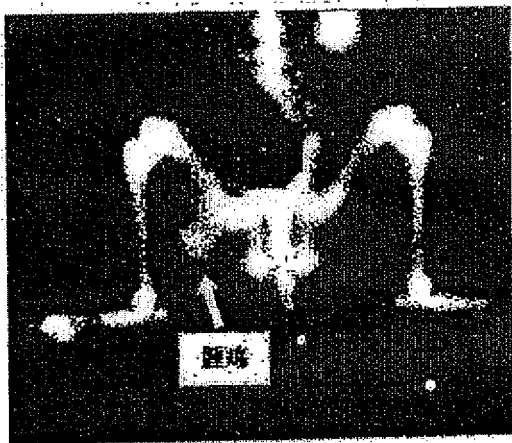
(57) Abstract

Problem To provide a radioactive compound capable of accumulating in primary tumors and bone metastatic tumors simultaneously and useful for imaging tumors, tumor therapy, etc.

Means for Solving Problem A radioactive compound, comprising a uridine 5'-phosphate derivative shown by the formula

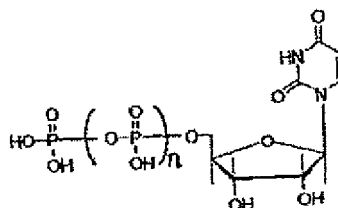


which is labeled with a radioactive metal nucleus such as technetium (^{99m}Tc), rhenium (^{186}Re , ^{188}Re), tin ($^{117\text{a}}\text{Sn}$), samarium (^{153}Sm), etc.; drugs, such as imaging agents, tumor therapeutic agents, pain emollients, etc., containing this compound; and a composition for preparing said radioactive compound.



Scope of the Patent Claims

1. Radioactive-labeled uridine derivative, comprising a uridine 5'-phosphate derivative shown by the formula

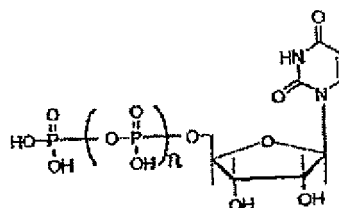


(in which n is 1 or 2), which is labeled by a radioactive metal nucleus.

2. Radioactive-labeled uridine derivative in accordance with claim 1, in which the uridine 5'-phosphate is a uridine 5'-diphosphate or a uridine 5'-triphosphate.

3. Radioactive-labeled uridine derivative in accordance with claim 1, in which the radioactive metal nucleus is technetium (^{99m}Tc), rhenium (^{186}Re , ^{188}Re), tin (^{117a}Sn), or samarium (^{153}Sm).

4. Composition for producing a radioactive-labeled uridine derivative which contains a uridine 5'-phosphate derivative shown by the formula



(in which n is 1 or 2) and a reducing agent for reducing the radioactive metal nucleus.

5. Composition for producing a radioactive-labeled uridine derivative in accordance with claim 4, in which the uridine 5'-phosphate is a uridine 5'-diphosphate and/or a uridine 5'-triphosphate and the reducing agent is stannous chloride or ascorbic acid.

6. Drugs containing radioactive-labeled uridine derivatives in accordance with claim 1.

7. Drugs in accordance with claim 6, which are tumor imaging drugs.

8. Drugs in accordance with claim 6, which are tumor therapy drugs.

9. Drugs in accordance with claim 6, which are pain emollient drugs for pain caused by bone metastatic tumors.

Detailed Description of the Invention

[0001]

Field of Industrial Application The present invention pertains to a radioactive-labeled uridine derivative. More specifically, it pertains to a radioactive-labeled uridine derivative obtained by labeling a compound, which has a nucleic acid part which shows an accumulatability in malignant

tumors with high nucleic acid demands as well as the metal nucleus chelating ability which the conventional phosphoric acid and polyphosphoric acid have, with radioactive metal nuclei such as ^{99m}Tc or ^{186}Re , ^{188}Re , ^{117a}Sn , ^{153}Sm , etc., and drugs containing this compound.

[0002]

Prior Art SPECT (single photon emission computed tomography) agents are used in the imaging diagnosis of malignant tumors in nuclear medicine. Examples of these agents that are already known are ^{67}Ga , ^{201}Tl , ^{99m}Tc (V)-DMSA, ^{131}I -adosterol, ^{131}I -MIBG, ^{99m}Tc -MIBI, ^{111}In -octreotide, etc. (*Kakuigaku [Nuclear Medicine]* 32: 1125-1130, 1995). Furthermore, ^{18}F -FDG, etc., are being used as PET (positron emission computed tomography) drugs.

[0003] However, these radioactive drugs show accumulation at tumor sites, and most of them reflect primary tumors. Among the radioactive drugs mentioned above, ^{201}Tl is known to accumulate in malignant tumors in bone and cartilage tissues and it is useful in diagnosing bone metastatic tumors, but the gamma ray energy of its nuclear species is comparatively weak and it has proven difficult to obtain clear images with it. Moreover, some original tumors metastasize to bones, etc., becoming bone metastatic tumors, and these bone metastatic tumors are imaged with ^{99m}Tc -MDP (methylene diphosphonate), a ^{99m}Tc -labeled phosphate compound. However, ^{99m}Tc -MDP does not show accumulating ability in primary tumors, and cannot image these tumors.

[0004] Furthermore, basic research and clinical trials have been performed on the tissue distributions and tumor intakes of ascites hepatoma AH109A-implanted rats by ^{18}F -5-FUR (^{18}F -5-fluorouridine), ^{18}F -5-FU (^{18}F -5-fluorouracil), and ^{18}F -5-FdUR (^{18}F -5-fluorodeoxyuridine), but they do not accumulate in the liver or kidneys and have been judged not to be suitable for diagnosing abdominal cancers (*Houshasen Igaku Taikei Pojitoron CT [Compendium of Radiology, Positron CT]*, p. 269, publ. Nakayama Shoten).

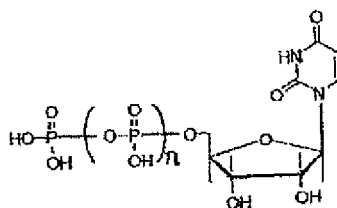
[0005]

Problem to be Solved by the Invention Therefore, there has been a demand for radioactive-labeled uridine derivatives which would be capable of accumulating in primary tumors and bone metastatic tumors simultaneously and would be useful for imaging tumors, tumor therapy, etc.

[0006]

Means for Solving the Problem The inventors researched the property of nucleic acid dependence of malignant tumors when they multiplied; as a result, they discovered that compounds with nucleic acid parts and phosphate parts can accumulate simultaneously in the primary tumors and bone metastatic tumors and perfected the present invention.

[0007] That is, the present invention provides a radioactive-labeled uridine derivative, comprising a uridine 5'-phosphate derivative shown by the formula



(in which n is 1 or 2), which is labeled by a radioactive metal nucleus, as well as drugs containing this compound as their active ingredient, which are imaging agents and pain emollient and therapeutic drugs.

[0008] Examples of the uridine 5'-phosphate derivatives shown by formula (I), which are the starting raw material of the radioactive-labeled uridine derivative of the present invention, are uridine diphosphate (UDP) and uridine triphosphate (UTP). These compounds are both publicly known and easily obtainable.

[0009] In producing the radioactive-labeled uridine derivative of the present invention by using these uridine 5'-phosphate derivatives (I), one can, for example, dissolve the uridine 5'-phosphate derivative (I), such as UDP or UTP, in a suitable solvent, such as water, and add a reducing agent of radioactive metal nuclei (referred to below as "radioactive metal reducing agent"), after which a radioactive metal nucleus solution with the necessary radioactive strength is added to this solution from a generator, etc. In this production process, it is desirable to make the pH acidic in order to increase the labeling rate of the radioactive metal nucleus solution.

[0010] Radioactive metal nuclei which can be used in producing the radioactive-labeled uridine derivative include technetium (^{99m}Tc), rhenium (^{186}Re , ^{188}Re), tin (^{117a}Sn), samarium (^{153}Sm), etc. Furthermore, stannous chloride or ascorbic acid, etc., can be used as the radioactive metal reducing agent.

[0011] The radioactive-labeled uridine derivative of the present invention may be used immediately after production by adding a radioactive metal nucleus solution to a mixture of the uridine 5'-phosphate derivative (I) and the radioactive metal reducing agent, as mentioned above, but it can also be produced by freeze-drying the aforementioned mixture of the uridine 5'-phosphate derivative (I) and the radioactive metal reducing agent to make a composition for producing the radioactive-labeled uridine derivative, to be prepared at the time of use (referred to below as "kit for preparation at the time of use"), and then adding the necessary quantity of the radioactive metal nucleus at the time of use.

[0012] This kit for preparation at the time of use can be produced by mixing a sufficient quantity of the uridine 5'-phosphate derivative (I) for making chelation possible with a specific quantity of the radioactive metal reducing agent and freeze-drying this mixture. In order to preserve the reducing ability after labeling with the radioactive metal nucleus, it is desirable to add a specific quantity of sodium thiosulfate salt, ascorbic acid or its sodium salt, potassium salt, etc. Also, any other desired ingredients, such as excipients, buffers, etc., may be included in the composition.

[0013] By using the kit for preparation at the time of use which is obtained in this way, it is possible to obtain the radioactive-labeled uridine derivative of the present invention, which can be used for imaging diagnosis or therapy of primary tumors and bone metastatic tumors anywhere and in a simple manner, using a radioactive metal nucleus source.

[0014]

Operation The radioactive-labeled uridine derivative of the present invention uses the property of the diphosphate or polyphosphate part, consisting of two or more phosphates, that it has a very strong chelating ability with respect to radioactive-labeled metal nuclei, such as ^{99m}Tc , ^{186}Re , ^{188}Re , ^{117a}Sn , and ^{153}Sm , and the property of the nucleic acid part, such as the pyrimidine or purine skeleton, of being easily incorporated in tumor parts.

[0015] Therefore, the radioactive-labeled uridine derivative of the present invention shows a behavior in the body which is very similar to ^{99m}Tc -MDP, and can detect bone pathologies such as bone metastatic tumors, and also is able to image primary tumor parts, which could not be imaged with ^{99m}Tc -MDP, so that it can be used at the same time to diagnose malignant tumors and bone metastatic tumors.

[0016]

Actual Examples The present invention will be explained in more detail below by giving actual examples, but it is not limited in any way by these examples.

[0017] **Actual Example 1**

Method for preparing technetium-labeled uridine derivative (1): 80 mg of UDP were added to 3.0 mL of physiological saline solution and stirred and dissolved, using a stirrer. 0.85 mg of ascorbic acid and 50 μL of stannous chloride dihydrate solution (15 mg/mL: 0.1 N HCl) were added to this solution, after which the pH was adjusted to 2 with 3N hydrochloric acid. Physiological saline solution was added to this solution to make the total quantity 5.0 mL; in this way, the composition solution for [adding] technetium was obtained. 1.0 mL of this solution was taken and 1.0 mL of sodium pertechnetate ($^{99m}\text{TcO}_4^-$) was added. The solution was stirred vigorously to perform the labeling, and ^{99m}Tc -UDP was obtained.

[0018] **Actual Example 2**

Method for preparing technetium-labeled uridine derivative (2): ^{99m}Tc -UDP was obtained in the same manner as in Actual Example 1, except that UTP was used instead of the UDP, and the quantity of ascorbic acid was changed to 0.21 mg.

[0019] **Actual Example 3**

Method for producing kit for preparing a radioactive-labeled uridine derivative: 80 mg of UDP and 0.85 mg of ascorbic acid were added to 3.0 mL of water for injection; this mixture was stirred, using a stirrer, to perform the dissolution. After 50 μL of stannous chloride dihydrate solution (15 mg/mL: 0.1 N HCl) were added to this solution, the pH was adjusted to 2 with 3N hydrochloric acid. Water for injection was added to the solution obtained to make the total quantity 5.0 mL. 1.0 mL of this solution was put into each of a number of 5-mL vials and freeze-drying was performed to obtain kits for preparing radioactive-labeled uridine derivative, as freeze-dried products.

[0020] **Actual Example 4**

Method for preparing technetium-labeled uridine derivative (3): 2.0 mL sodium pertechnetate ($^{99m}\text{TcO}_4^-$) were added to the freeze-dried kit for preparing a radioactive-labeled uridine derivative which was obtained in Actual Example 3 and stirring was performed, to obtain ^{99m}Tc -UDP.

[0021] **Actual Example 5**

Radiological purity test of technetium-labeled uridine derivatives
Test method:

Radiological purity test by thin-layer chromatography (TLC):

As the thin layer plate, a Merck Co. TLC plate (Silica-Gel 60F₂₅₄) was used, and as the developing solution, 2-butanone was used. The TLC tests were performed on the ^{99m}Tc labeling agents obtained in Actual Examples 1 and 2, according to the "Methylene diphosphonate-technetium (Tc-99m) injection solution [MDP]."

[0022] In these TLC tests, the target substances ^{99m}Tc-UDP or ^{99m}Tc-UTP stopped at the origin. In contrast, the unbonded sodium pertechnetate developed to Rf 1.0. Therefore, the radiological purity of the Tc-99m labeling agent was obtained from the following formula.

[0023]

Radiological purity (%) = (A₁/A₂) x 100

where A₁: Peak quantity of radioactivity near the origin
 A₂: Total quantity of radioactivity of thin layer plate

[0024] **Results** The radiological purities of the ^{99m}Tc-UDP of Actual Example 1 and the ^{99m}Tc-UTP of Actual Example 2, obtained by means of this formula, were very high, as shown in Table 1.

[0025]

Table 1

| Elapsed time | Radiological purity (%) | |
|----------------------------|-------------------------|-----------------------|
| | ^{99m} Tc-UDP | ^{99m} Tc-UTP |
| Immediately after labeling | 99.1 | 98.9 |
| After 6 hours | 98.3 | 98.7 |
| After 24 hours | 98.2 | 99.2 |

[0026] Actual Example 5

Tumor imaging of model animal:

(1) VX-2 tumor cells were implanted into the muscle tissue of a rabbit near the femur, and cancer cells were thoroughly grown. 55.5 MBq/400 μL of the ^{99m}Tc-UDP obtained in Actual Example 1 were administered to the rabbit; after 2 hours, imaging was performed with a gamma camera. As a result, it was confirmed by the image that the ^{99m}Tc-UDP had accumulated in the normal part of the bone and the kidneys, as well as the tumor of the implant part (Figure 1).

[0027] (2) For comparison, on the other hand, VX-2 tumor were implanted into a rabbit in the same manner as described above and cancer cells were thoroughly grown, after which a ^{99m}Tc-MDP solution, a publicly known bone imaging agent, was administered at 55.5 MBq/400 μL. Imaging was performed 1 hour and 2 hours after the administration; no accumulation was seen in the tumor (Figure 2).

[0028] After waiting for 2 days for the decay of the ^{99m}Tc, 55.5 MBq/400 μL of ^{99m}Tc-UDP were administered to the same rabbit. Imaging was performed 1 hour and 2 hours after the administration; it was confirmed that the ^{99m}Tc-UDP accumulated in the tumor at the implantation part, where accumulation was not seen with the bone imaging agent at either time (Figure 3). These

facts clearly showed that ^{99m}Tc -UDP could image both the primary tumor and the bone metastatic tumor, compared with ^{99m}Tc -MDP, which has been used up to now.

[0029] **Actual Example 6**

Distribution in bodies of normal rats: ^{99m}Tc -UDP was administered to 8 normal rats at 2.46 MBq/200 μL and the distributions in the body after 1 hour and 2 hours were investigated. Since it was confirmed that the principal sites of accumulation in the normal animals were in the bones and kidneys, these sites, as well as the liver and blood were removed and measured. For comparison, ^{99m}Tc -MDP was used. The results are shown in Tables 2 and 3.

[0030]

Table 2

| | ^{99m}Tc -UDP | | ^{99m}Tc -MDP | |
|---------|------------------------|---------|------------------------|---------|
| | 1 hour | 2 hours | 1 hour | 2 hours |
| Blood | 0.3047 | 0.2215 | 0.0901 | 0.0526 |
| Tibia | 3.5095 | 3.5457 | 3.9188 | 3.5764 |
| Liver | 0.1494 | 0.0948 | 0.0285 | 0.0215 |
| Kidneys | 2.4746 | 2.8058 | 0.4348 | 0.3796 |

(The figures in the table show % dose/g)

[0031]

Table 3

| | | ^{99m}Tc -UDP | ^{99m}Tc -MDP |
|---------|------------------|------------------------|------------------------|
| 1 hour | % dose (tibia) | 3.5095 | 3.9188 |
| | % dose/g (blood) | 0.3047 | 0.0901 |
| | tibia/blood | 11.519 | 43.507 |
| 2 hours | % dose (tibia) | 3.5457 | 3.5764 |
| | % dose/g (blood) | 0.2215 | 0.0526 |
| | tibia/blood | 16.008 | 68.027 |

[0032] As is clear from these results, the bone accumulation of ^{99m}Tc -UDP, the radioactive-labeled uridine derivative of the present invention, showed a similar behavior to ^{99m}Tc -MDP, a bone imaging agent.

[0033]

Effectiveness of the Invention The radioactive-labeled uridine derivative of the present invention makes possible simultaneous imaging of primary tumors and bone metastatic tumors; in addition, like conventional bone imaging agents, it has some ability to accumulate in normal bone. Therefore, it clearly shows the boundaries of the disease and is useful for grasping the sites of primary tumors in the body. Therefore, it can provide excellent images.

[0034] Moreover, since the radioactive-labeled uridine derivative of the present invention accumulates simultaneously in primary and bone metastatic tumors, it can be used as a tumor therapy agent which selectively destroys only the tumors, by selecting and using suitable

radioactive nuclei. Furthermore, since this radioactive-labeled uridine derivative accumulates in bone metastatic tumors, it can also be used as a pain-alleviating agent for lessening pain produced by these tumors.

Brief Description of the Figures

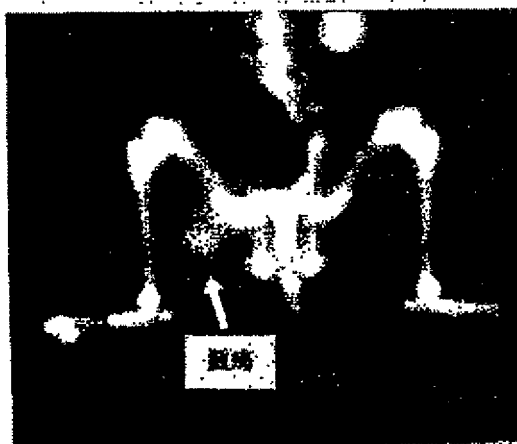
Figure 1 is a photograph showing the results of imaging 2 hours after the administration of the radioactive-labeled uridine derivative of the present invention (^{99m}Tc -UDP) in a rabbit to which VX-2 cancer cells were implanted.

Figure 2 is a photograph showing the results of imaging 2 hours after the administration of a comparison compound (^{99m}Tc -MDP) in a rabbit to which VX-2 cancer cells were implanted.

Figure 3 is a photograph showing the results of imaging 2 hours after the administration of the radioactive-labeled uridine derivative of the present invention (^{99m}Tc -UDP) in the rabbit of Figure 2, after the first administration of the comparison compound.

Figure 1

(Photograph substituted for drawing)



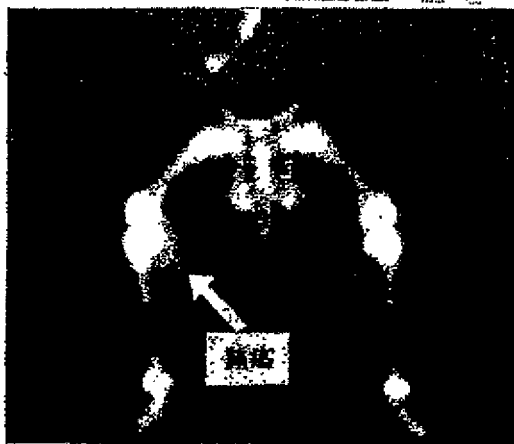
(Japanese in photograph: "tumor")

Figure 2

(Photograph substituted for drawing)



Figure 3
(Photograph substituted for drawing)



(Japanese in photograph: "tumor")